REMARKS

Compliance with Sequence Rules

On page 2 of the Office Action, the Examiner states that the sequences are disclosed in the specification at page 36, line 32 and page 52, line 27 without sequence identification number.

Applicants submit that the Specification is amended as described supra. Applicants submit that based on the amendment to the paragraphs, the specification is now compliant with the Sequence Rules as stated by the Examiner.

Status of the Claims

Claims 1-85 are pending. Claims 2-5, 34-70 and 76-85 are withdrawn. Claims 1, 6-33 and 71-75 stand rejected. Claims 1 and 10 are currently amended. Claim 9 is canceled herein. No new matter is added to the amended claim.

Election/Restriction

On page 2 of the Office Action, the Examiner states that claims 2-5, 34-70 and 76-85 are withdrawn because the claims are not linked by a special technical feature as explained in the election/rejection Office Action, and further evidenced in the rejection heading under 35 U.S.C. §102 as explained in the instant Office Action. Applicants respectfully traverse this withdrawal.

Applicants state that the special technical feature linking the Groups 1-32 is the conformational flexibility of the pCRA and pCRAW antigens. Applicants submit that this unifying special technical feature is vital for coordinated alignment of the electrophilic and noncovalent binding sites of the antigens, respectively, with the complementary nucleophilic and noncovalent binding sites of the antibody as explained in paragraph 010 of the instant specification as published.

Applicants submit that the prior art does not teach this unifying special technical feature. **Taguchi** et al is restricted to a small peptide antigen in which the electrophile is located at the C-terminus. This does not allow optimal coordinated alignment between the interacting subsites of antigen and antibody. Additional arguments regarding the inapplicability of **Taguchi** et al to predict the instant invention or render it obvious are presented in the 35 U.S.C. §102 heading vide infra. Based on this, Applicants submit that the present invention is useful to prepare pCRA and pCRAW antigens.

Additionally, the Applicants submit that an inventive concept in the claims identified in Groups 1-32 is that the Y'-Y''=Y' component contains a flexible electrophile Y that forms a full or partial covalent bond with the nucleophile of the antibody as defined in Paragraph 0087 of the instant specification. The reaction is coordinated with non-covalent binding between the antibody and the antigenic determinant. The prior art search would only necessitate searching Y'-Y''=Y' component regardless of the structure of L1...Lx...Lm and Lx-L'. Accordingly, Applicants respectfully request that Groups 1-32 be examined together.

Based on this, Applicants respectfully submit that claims 2-5, 34-70 and 76-85 be rejoined to claims 1, 6-33 and 71-75.

Claim amendments

Claim 1 is amended to overcome the 35 U.S.C. §112, first paragraph (enablement and written description) and 35 U.S.C. §112, second paragraph rejections. Amended claim 1 encompasses the limitations of claim 9 canceled herein. Amended claim 1 is drawn to a method of preparing antibodies that bind polypeptide antigens covalently and catalyze cleavage of peptide bonds in a polypeptide antigen. The method comprises producing in an organism, antibodies to a covalently reactive polypeptide antigen analogue (pCRA). The pCRA comprises an amino acid that has a functional group to which, by means of an atom, covalent bond or linker, is attached a covalently reactive electrophilic group that reacts specifically with an antibody that binds to the amino acid assembly. This amendment is supported by the instant specification specifically Fig 2 as described on page 5, line 32- page 6, line 8 and Example 1, specifically Fig 7, Fig 8, Fig 9 as described on page 7, line 9- page 8, line 16.

Claim 10 is amended to depend from claim 1 and no longer depend from claim 9 which is canceled herein.

The 35 U.S.C. §112, Second Paragraph Rejection

Claims 1, 6-33 and 71-75 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Applicants respectfully traverse this rejection.

On page 3 of the Office Action, the Examiner states that claim 1 is indefinite in reciting covalent antibodies as it is unclear what covalent antibodies mean because claim 1 produces catalytic antibodies using pCRA.

Claim 1 is amended as described supra to recite 'covalent antibodies that form complexes with polypeptide antigens' and 'catalytic antibodies'. Applicants submit that 'catalytic

antibodies' is supported by the instant specification and as explained by the Examiner on page 3 of the Office Action.

Covalent antibodies as recited in amended claim 1, encompass antibodies that form complexes with polypeptide antigens wherein said complexes do not dissociate on treatment with a protein denaturant. The same is supported by the instant specification. Specifically, Figures 41 and 42 shows binding of gp120 by monoclonal antibodies produced by immunization with a pCRA. The antigen used in these figures is the natural gp120 polypeptide (which is devoid of artificial electrophilic groups contained in pCRAs). Applicants submit that the complexes formed by the monoclonal antibodies were not dissociated by sodium dodecyl sulfate, indicating irreversible antibody binding due to the covalent reactivity of the antibodies. It is known in the art that sodium dodecyl sulfate can dissociate non-covalent complexes formed by conventional antibodies with polypeptide antigens. Additionally, Figure 42 clearly shows that complexes formed by conventional antibodies to gp120 were dissociated by sodium dodecyl sulfate. Based on this, the monoclonal antibodies would be considered covalent antibodies by a person having ordinary skill in this art. As explained in paragraph 0008 of the instant specification, covalent reactivity of these covalent antibodies is due to their increased nucleophilic reactivity attained by immunization with electrophilic pCRAs. Covalent antibodies are also supported by Example VI in the instant specification as described on paragraphs 0525 and 0526 of the instant application.

Applicants further submit that the mechanism whereby pCRAs and pCRAWs induce the production of antibodies that react covalently with the natural polypeptide antigen is explained in paragraph 0099 of the specification. Specifically, the following lines from paragraph 0099 describe covalent antibodies "Thus, antibodies displaying high noncovalent binding affinity and rapid covalent reaction with pCRAs also display high affinity and covalent reactivity with the targeted natural protein. Antibodies that bind covalently to the natural protein inactivate the latter molecule permanently. In comparison, ordinary noncovalent antibodies dissociate from antigen-antibody complexes, regenerating biologically effective antigen."

The distinction between the 'catalytic antibodies' and 'covalent antibodies' in amended claim 1 is described in paragraph 0083 of the instant specification. Specifically, 'covalent reactivity is a necessary but not sufficient condition for catalysis. This is because completion of the catalytic cycle requires facilitation of events occurring after formation of the covalent acyl-enzyme intermediate, i.e., hydrolysis of the intermediate and release of product peptides. Nucleophilic proteins devoid of this capability will not express catalytic activity. Therefore, only a subset of nucleophilic Abs are anticipated to express catalytic activity.' Based on this, applicants submit that

the instant specification supports 'catalytic antibodies' as explained by the Examiner, and also 'covalent antibodies' as defined in amended claim 1, and described supra.

Applicants submit that the nature of covalent bonds formed by the 'covalent antibodies' is explained in Paragraph 0087 of the instant specification. Specifically, "In the extreme case, increased nucleophilicity could result in formation of a full covalent bond with the antigen. A lesser manifestation is the formation of partial covalent bonds by resonant electron sharing mechanisms (see Fig 1; a familiar example of a weak bond with partial covalent character is the hydrogen bond)." Example X, as described in Paragraphs 0590 and 0598 of the instant specification, describes covalent antibodies raised to yet another pCRA, Aβ1-42-CRA.

Accordingly, based on this amendment and remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 6-8, 10-33 and 71-75 under 35 U.S.C. §112, second paragraph.

The 35 U.S.C. §112, First Paragraph Rejections

Claims 1, 6-7, 11-12, 15-23, 25-29, 71-75 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

On page 3 of the Office Action, the Examiner states that claims 1, 6-7, 11-12, 15-23, 25-29, 71-75 are directed to a method of generating catalytic antibodies to polypeptide covalently reactive antigen (pCRA) wherein said pCRA comprise any antigenic polypeptide covalently attached to any transition state analog of any reaction and injecting said antigen to any organism wherein said antibodies produced shows catalytic activity of any enzyme. The Examiner argues that the prior art and the specification teach pCRAs that produce catalytic antibody having protease activity that cleaves peptide bonds. The Examiner further states that the specification indicates that "A potential weakness is that immunogen does not contain structural feature favoring synthesis of Abs capable of rapid hydrolysis of the acyl-Ab-intermediate and product release". The Examiner states that the specification does not disclose how catalytic antibodies produced by any pCRA comprising any polypeptide epitope can show catalytic activity of any enzyme. The Examiner concludes that given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recogonize that applicants were in possession of the claimed invention.

Claim 1 is amended as described supra and no longer recites catalytic antibodies possessing catalytic activity of any enzyme. Applicants submit that as recommended by the Examiner, amended claim 1 recites only covalent and catalytic antibodies directed to polypeptide antigens. Antibodies directed to other types of antigens have been excluded, i.e., lipids, carbohydrates and nucleic acids.

Applicants submit that the method of preparing covalent antibodies to polypeptide antigens as recited in amended claim 1 is supported by the instant specification, specifically paragraph 0099 as described supra. The method of preparing catalytic antibodies to catalyze cleavage of peptide bonds in a polypeptide antigen as recited in claim 1 is supported by the instant specification and the prior art and as described by the Examiner on page 4 of the Office Action. Further, as described by the Examiner on page 5 of the Office Action, the specification supports methods of generating catalytic antibodies to the antigen comprising pCRA wherein said catalytic antibodies cleave the peptide bonds of polypeptide molecules. Additionally, Applicants submit that as described by the Examiner on page 6 of the Office Action, the instant specification and the prior art recite the method of producing catalytic antibodies that cleave peptide bonds in a polypeptide molecule as recited in claim 1.

Applicants submit that the many examples of electrophilic pCRA structures adequately encompass the genus of nucleophilic antibodies with covalent and catalytic activity recited in claim 1. This is supported by the instant specifications and the prior art. Applicants respectfully state that the entire genus of antibodies recited in claim 1 is unified by a single characteristic, that is, they possess the nucleophilic activity found in the serine protease family of proteins. This entire genus of antibodies has been demonstrated to react with pCRAs in the instant invention. Specific examples include the covalent and catalytic antibodies directed to gp120 (Figure 16 and Example 2), Aβ peptide (Figure 47 and 48 and Example 10), VIP (Figure 21 and Example 3) and EGFR (Figure 12 and Example 1). Additionally, there are several reports in the literature from other researchers indicating that catalytic antibodies that hydrolyze peptide bonds in additional polypeptides also display serine protease type of nucleophilic reactivity, for example catalytic antibodies to Factor VIII, to myelin basic protein and to HIV Integrase. Based on this, Applicants submit that covalent and catalytic to diverse polypeptides can be raised by immunization with the class of pCRAs recited in claim 1.

Accordingly, based on this amendment and remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 6-7, 11-12, 15-23, 25-29, 71-75 under 35 U.S.C. §112, first paragraph.

Claims 1, 6-7, 11-12, 15-23, 25-29, 71-75 are rejected under 35 U.S.C. §112, first paragraph as being non-enabled. Applicants respectfully traverse this rejection.

On page 5 of the Office Action, the Examiner states that claims 1, 6-7, 11-12, 15-23, 25-29, 71-75 are rejected because the specification, while being enabling for method of generating catalytic antibodies to the antigen comprising pCRA wherein said method comprises administering said pCRA to an organism such as mouse and wherein said catalytic antibodies cleave the peptide bond of protease type polypeptide molecule, does not reasonably provide enablement for method of generating catalytic antibody that shows catalytic activity of any enzymatic reaction. The Examiner states that since production of catalytic antibodies dependent on the structure of TS, and enzymatic reaction depends on mimicking the TS of bond cleavage or formation of that reaction, as the specification does not teach structures of all the constituents of pCRA claimed, the specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is amended as described supra. Applicants submit that as described by the Examiner on page 5 of the Office Action, the specification supports methods of generating catalytic antibodies to the antigen comprising pCRA wherein said catalytic antibodies cleave the peptide bond of protease type polypeptide molecules.

Applicants respectfully submit that the catalytic antibodies disclosed in the instant specifications meet the criteria for a proteolytic enzyme based on the definition of a proteolytic enzyme, i.e., the antibodies hydrolyze peptide bonds and a single antibody molecule can be reused for repeated reaction cycles. Specifically, Figure 17 as described in Example 2 and Figure 47 as described in Example 10 of the instant specification demonstrate peptide bond hydrolysis. Additionally, repeated use of the antibody for multiple reaction cycles has been disclosed. For instance, Example 2 as described in Paragraph 0274 discloses: "Twelve mol E-A-R-MCA were cleaved per mole MAb YZ20 over the course of the reaction (22 h), indicating that the MAb is capable of turnover, a defining feature of a catalyst." Additionally, Example 4, Paragraph 0399 discloses: "Apparent turnover numbers (k_{cat}) for the IgM preparations were as high as 2.8/min." The small K_m values of the disclosed catalytic antibodies are helpful in attaining high reaction rates comparable to conventional enzymes. For instance, Example IV, Paragraph 0377 teaches: "Some catalytic Abs express catalytic efficiencies (k_{cat}/K_m) comparable to conventional enzymes, but this is due to high affinity recognition of antigen ground state."

Applicants submit that the instant specification discloses methods to obtain efficient catalytic antibodies using the pCRAs of the present invention. For example, Example 10, Paragraph 0606 discloses the use of one the pCRAs for this purpose as follows: "An alternative

way to identify high turnover catalysts is by flow cytometric sorting of nucleophilic B cells labeled with Aβ-CRAs, followed by application of the hybridoma methods."

Applicants respectfully submit that the utility of the pCRAs disclosed in the present invention in isolating efficient catalytic antibodies is supported by other publications in the art. For example, one of the pCRA variants described in Example 10, Aβ-CRA, is used to isolate exceptionally efficient proteolytic antibodies to Aβ peptide. Antigens similar to the pCRAs have been recently used to produce catalytic antibodies to gp120.

Accordingly, based on the instant specification and remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 6-7, 11-12, 15-23, 25-29, 71-75 under 35 U.S.C. §112, first paragraph.

Claims 1, 6-7, 11-12, 15-23, 25-29, 71-75 are rejected under 35 U.S.C. §112, first paragraph as being non-enabled. Applicants respectfully traverse this rejection.

On page 6 of the Office Action, the Examiner states that claims 1, 6-7, 11-12, 15-23, 25-29, 71-75 are rejected because the claims encompass methods of generating catalytic antibodies by any pCRA comprising any antigenic polypeptide covalently attached to any covalently reactive electrophilic group and inducing said antigen in any organism and wherein said antibodies show catalytic activity of any enzyme. The Examiner further states that the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods of generating catalytic antibodies having any type of transition state that mimic the transition state of any enzymatic reaction. The Examiner states that these claims drawn to methods of generating catalytic antibodies that show catalytic activity of any enzyme. Examiner argues that the prior art and the specification teach pCRAs producing catalytic antibodies eliciting transition state of a protease type bond cleavage that cleave peptide bond in a protease type polypeptide molecule. The Examiner argues that the specification or the prior art neither describes all the structures of the components of the pCRA and nor teach how catalytic antibodies produced by said pCRA can show catalytic activity of any enzyme. Based on this, the Examiner concludes that in view of the great breadth of the claims, the amount of experimentation required to elicit antibodies and screening to isolate catalytic antibody molecules that show the desired catalytic activity of any reaction and the lack of guidance, working examples, unpredictability of the art in predicting the function from protein's structure, the claimed invention would require undue experimentation.

Claim 1 is amended as described supra and no longer recite catalytic antibodies produced pCRA, possessing catalytic activity of any enzyme. Applicants submit as described by

the Examiner on page 6 of the Office Action, the instant specification and the prior art recite the method of producing catalytic antibodies that cleave peptide bonds in a polypeptide molecule as recited in claim 1.

Applicants respectfully submit that neither **Mader et al.** (Chem Rev. 1997, 97, 1281-1301) or **Chica et al.** (Curr Opin Biotechnol. 2005 Aug; 16(4):378-84) are relevant to enablement of the present invention. pCRAs are not negatively charged transition state analogs as described by **Mader et al.** or **Chica et al.** An essential feature of transition state analogs is that they must contain a negatively charged oxyanion that mimics the oxyanion formed in the transition state of the catalytic reaction. The oxyanion is required to bind the 'oxyanion hole' of enzymes and certain esterase antibodies, as described by **Mader et al** and **Chica et al.** In contrast, pCRAs do not mimic the structure of the negatively charged oxyanion in the catalytic pathway. Indeed, pCRAs of the present invention can be neutral or positively charged compounds. Binding to the 'oxyanion hole' is not a requirement for the mechanism of pCRAs. Furthermore, pCRAs are structural mimics of the entire electrophilic reaction center in the polypeptide epitope. pCRAs contain an electrophilic phosphorus atom that mimic the electrophilic carbonyl groups of polypeptides. The electrophilic phosphorus atom reacts covalently with nucleophilic catalytic sites in antibodies. The covalent reaction occurs in coordination with noncovalent binding of the peptide epitope in pCRAs by the antibody catalytic sites. Applicants submit that as displayed in Figure 14B, the phosphorus atom of the pCRA in tope reaction scheme of Figure 14B reacts covalently with antibody nucleophile ('Nu' in the figure) and forms a covalent bond. Noncovalent recognition of the pCRA is shown by broken lines connecting the peptide epitope (Ag) of the pCRA and the antibody (Ab). Applicants submit that as can be seen from the figure, the foregoing remarks and other instant specifications, pCRAs and transition state analogs are structurally and functionally distinct entities.

Additionally, the immunological approach of **Mader et al.** and **Chica et al.** differs from the approach described in the present invention. Applicants respectfully note that there is no validated example of a proteolytic antibody generated by immunization with the transition state analogs described by **Mader et al** and **Chica et al.** Applicants submit that this is described in Paragraph 0082 of the instant specification. In contrast, the pCRA approach has been validated for generation of proteolytic antibodies.

Mader et al. and **Chica et al.** do not recognize the existence of nucleophilic catalytic antibodies present in the preimmune repertoire encoded by germline antibody genes. Instead they rely solely on adaptive diversification of antibody sequences for de novo formation of catalytic antibodies following immunization with transition state analogs. In contrast, the pCRA approach in the present invention exploits the existence of pre-existing serine protease-like

antibodies in the preimmune repertoire encoded by germline antibody genes. Indeed, the structure of the pCRAs was specifically designed to enable their reaction with the germline-encoded antibodies. Immunization with pCRAs improves the catalytic efficiency of the pre-existing antibodies by adaptive B cell clonal selection. The instant specification clarifies the importance of the preimmune, germline encoded antibody catalytic activity in the pCRA approach. Specifically, Example 4 and Example 5 show the existence of the preimmune catalytic antibodies.

The failure of the transition state analogs and the success of pCRAs in raising proteolytic antibodies is discussed in Paragraph 0091 of the instant specification-

"As noted previously, immunization with negatively charged (oxyanionic) haptenic TSAs allows induction of esterase but not proteolytic Abs (21,22). In comparison, success in inducing proteolytic Abs by the compounds disclosed in the present application can be understood from recruitment of the innate forces utilized by Abs in their interactions with the antigen, that is, nucleophilic reactivity coordinated with noncovalent binding at epitope constituents distant from the reaction center."

Accordingly, based on the instant specifications and remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 6-7, 11-12, 15-23, 25-29, 71-75 under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §102 Rejections

Claims 1, 8-14, 16, 24 and 31 are rejected under 35 U.S.C. §102 (a) as being anticipated by **Taguchi et al** (*Bioorg and Med. Chem. Lett.* 2002, 3167-3170). Applicants respectfully traverse this rejection.

On page 7 of the Office Action, the Examiner states that **Taguchi** et al teach a catalytic antibody raised by using gp120 polypeptide epitope (L of claim 1 having carboxyl functional group of amino acid residue as "Y") attached covalently to phosphonate ester (Y reactive electrophilic group, Transition state analogue) which comprise covalently reactive antigen (pCRA) and wherein said phosphonate ester moiety bind to the antibody and method of producing said antibody by including said pCRA to mouse.

Claim 1 is amended as described supra and is drawn to a method of preparing catalytic antibodies to catalyze cleavage of peptide bonds in a polypeptide antigen. The method comprises producing in an organism, antibodies to a covalently reactive polypeptide antigen analogue (pCRA). The pCRA comprises an amino acid that has a functional group to which, by means of an atom, covalent bond or linker, is attached a covalently reactive electrophilic group that reacts specifically with an antibody that binds to the amino acid assembly.

Taguchi et al teaches only a naturally occurring catalytic antibody light chain from a multiple myeloma patient that binds the peptidyl phosphonate ester, not a catalytic antibody raised by immunization with the peptidyl phosphonate ester. **Taguchi et al** teaches the covalent binding of a peptidyl phosphonate ester to the nucleophilic site of a naturally occurring catalytic antibody light chain from a multiple myeloma patient (light chain LAY). In addition, **Taguchi et al** teaches the covalent binding of the peptidyl phosphonate ester to non-catalytic antibodies raised by immunization with a non-electrophilic peptide epitope (residues 421-436). Therefore, **Taguchi et al** only teaches that the peptidyl phosphonate ester can serve as a specific detection reagent for the aforementioned antibodies. **Taguchi et al** does not teach covalent or catalytic antibodies raised by immunization with the peptidyl phosphonate ester or the pCRA of the present invention.

Applicants submit that the electrophilic group in the pCRA and the peptidyl phosphonate ester taught by **Taguchi et al** are not a transition state analog. Applicants submit that **Taguchi et al** does not teach the utilization of pCRAs for inducing the synthesis of antibodies with improved nucleophilicity. As nucleophilicity is rate-limiting in proteolysis, its enhancement would permit more rapid bond cleavage. Applicants submit that the art is deficient in methods for inducing the synthesis of proteolytic antibodies. Prior attempts to program structure of catalytic sites in antibodies have relied on non-covalent stabilization of the oxyanionic transition state (i.e., by immunization with transition state analogs). No antibodies with proteolytic activity have been raised by these means. The Applicants submit that **Taguchi et al** only teaches a peptidyl phosphonate ester that binds to the nucleophilic sites of natural proteolytic Abs covalently, but does not teach or motivate one in the art to design a method of synthesizing Abs with improved nucleophilicity utilizing pCRAs that serve as covalently reactive analogs for the same. The Applicants submit that **Taguchi et al** does not render obvious the instant invention as a person with ordinary skill in this art would not have a reasonable expectation that the claimed invention would work successfully.

To anticipate amended independent claim 1 and dependent claims 8, 10-14, 16, 24 and 31, **Taguchi et al.** must teach every element recited in the instant claims. Based on this, Applicants submit that Taguchi et al. does not identify the claimed invention.

Applicants submit that there are several structurally differences between the peptidyl phosphonate ester taught by Taguchi et al and the pCRAs of the present invention. First, the teaching of **Taguchi et al** is limited to a single electrophilic antigenic epitope within a small peptide produced by peptide synthesis. The genus of pCRAs in the present invention includes large proteins containing many electrophilic epitopes, in which the electrophile is attached to individual epitopes on the side chains of various amino acids. One skilled in the art is aware that large proteins cannot be synthesized by purely chemical synthetic methods. Moreover, it is not

possible to produce the post-translationally modified versions of native proteins by chemical synthetic means. In contrast, pCRAs can be prepared by modification of proteins that have been assembled by natural means, e.g., proteins purified from blood or from supernatants of cultured cells. Therefore, the pCRAs have substantially greater utility than the peptidyl phosphonate ester taught by **Taguchi et al.**

Secondly, the teaching of **Taguchi et al** is limited to a linear electrophilic epitope composed of contiguous amino acids. The genus of pCRAs in the present invention includes conformational (discontinuous) electrophilic epitopes composed of spatially neighboring amino acids that are distant from each other in the linear sequence (represented as L1---Lx---Lm in the pCRA formula). For one skilled in the art, it is clear that the vast majority of antigenic epitopes in proteins are conformational epitopes. Therefore, the pCRAs have substantially greater utility than the peptidyl phosphonate ester taught by **Taguchi et al.**

Thirdly, **Taguchi et al** only teaches a peptidyl phosphonate ester containing the electrophilic group located at the C terminus of the peptide. **Taguchi et al** does not teach incorporation of the electrophilic group in a side chain functional group of the amino acids of a polypeptide. This is a central difference enabling the pCRA technology. One skilled in the art is aware that incorporation of the electrophilic group in the side chain of one or more amino acid within the polypeptide or in the side chain of the N and C terminal amino acids is readily attainable. In contrast, **Taguchi et al** teaches incorporation of the electrophilic group at the C terminal carboxyl group of a small peptide by total chemical synthesis. As described in the foregoing remarks, it is not possible to prepare large proteins with an electrophilic group at the C terminus by total chemical synthesis.

Additionally, the structure of the peptidyl phosphonate ester taught by **Taguchi et al** is described by the formula of pCRA stated in claim 1 only if L' is defined as the C terminal carboxyl group of a peptide. The structure of the peptidyl phosphonate ester taught by **Taguchi et al** is not described by the formula of pCRA stated in amended claim 1 wherein L' is a side-chain functional group of Lx. Based on this, it can be stated that **Taguchi et al** does not teach a method to raise catalytic antibodies using a pCRA.

Based on this, Applicants submit that **Taguchi et al.** does not identify the claimed invention. The Applicants also submit that **Taguchi et al.** does not render obvious the instant invention as a person with ordinary skill in this art would not have a reasonable expectation that the claimed invention would work successfully. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 8, 10-14, 16, 24 and 31 under 35 U.S.C. §102(a).

Claims 1, 8-14, 16-18, 21-22, 24-29, 71-72 and 74 are rejected under 35 U.S.C. §102 (a) as being anticipated by **Paul et al** (US 6235714). Applicants respectfully traverse this rejection.

On page 8 of the Office Action, the Examiner states that **Paul et al** teaches catalytic antibody and method of producing said antibody by inducing CRAA to an organism wherein CRAA comprise polypeptide epitope attached covalently to phosphonate ester which comprise covalently reactive antigen (pCRA). The Examiner also states that **Paul et al** also teaches that the antigen molecule comprise tumor necrosis factor, epidermal growth factor receptor, gp120 etc and state that catalytic antibodies produced by said antigens can be used for the treatment of medical disorders like cancer, autoimmune diseases.

Claim 1 is amended as described supra. Applicants submit that **Paul et al** teaches covalently reactive antigen analog (CRAA), comprising 3-10 contiguous amino acids forming an epitope of a target antigen and further comprising a positively charged amino acid residue and an electrophilic reaction center. Applicants respectfully submit that the structure and utility of pCRAs from the instant invention are distinct and different from the CRAA taught by **Paul et al**. The pCRA of the present invention and CRAA taught by **Paul et al** are structurally distinct entities with differing reactivity to antibodies. Therefore, the antibodies produced and isolated using the pCRA of the present invention differ in their properties compared to the antibodies produced and isolated using the CRAA taught by **Paul et al**.

Applicants submit that **Paul et al** teaches a covalently reactive antigen analog (CRAA), comprising 3-10 contiguous amino acids forming an epitope of a target antigen and further comprising a positively charged amino acid residue and an electrophilic reaction center. The genus of pCRAs in the present invention includes conformational (discontinuous) electrophilic epitopes composed of spatially neighboring amino acids that are distant from each other in the linear sequence (represented as L1---Lx---Lm in the pCRA formula). For one skilled in the art, it is clear that the vast majority of antigenic epitopes in proteins are conformational epitopes. Based on this, Applicants submit that the pCRAs of the instant invention have substantially greater utility than the CRAA taught by **Paul et al**. Further, **Paul et al** does not teach a pCRA in which any amino acid that has a functional group to which, by means of an atom, covalent bond or linker, is attached a covalently reactive electrophilic group. Applicants submit that **Paul et al** only teaches positively charged amino acids on the N terminal side of the electrophilic group. In comparison, a pCRA can contain the electrophilic group placed neighboring a positive, neutral or negative charged amino

acid. In addition, **Paul et al** does not teach water-binding groups and optional charged or neutral groups that enhance binding affinity and specificity.

Additionally, the CRAA taught by **Paul et al** must contain the electrophilic group within the peptide backbone as a replacement of a peptide bond in the polypeptide antigen. **Paul et al** does not teach incorporation of the electrophilic group in a side chain functional group of the amino acids of a polypeptide. In contrast, the electrophilic group is located on the side chain functional group of any amino acid in the pCRA of the present invention. Thus, the teaching of **Paul et al** is limited to a single electrophilic antigenic epitope within a small peptide produced by peptide synthesis. The genus of pCRAs in the present invention includes large proteins containing many electrophilic epitopes. One skilled in the art is aware that incorporation of the electrophilic group in the side chain of one or more amino acid within the polypeptide is readily attainable. As the electrophilic group is attached to the side chains of various amino acids, a pCRA can be prepared from large proteins. One skilled in the art is aware that large proteins cannot be synthesized by purely chemical synthetic methods. Moreover, it is not possible to produce the post-translationally modified versions of native proteins by chemical synthetic means. In contrast, pCRAs can be prepared by modification of proteins that have been assembled by natural means, e.g., proteins purified from blood or from supernatants of cultured cells. Therefore, the pCRAs have substantially greater utility than the CRAA taught by **Paul et al**.

Applicants also submit that the ability to raise and isolate covalent and catalytic antibodies using pCRAs that contain the electrophilic group on a side chain functional group of a polypeptide is a vital aspect underlying the present invention. The importance of this is described in the instant specification in Example 2, Paragraphs 0262 and 0263. As explained supra, the CRAA taught by **Paul et al** do not contain the electrophilic group on a side chain functional group of a polypeptide.

To anticipate amended independent claim 1 and dependent claims 8, 10-14, 16, 24 and 31, **Paul et al.** must teach every element recited in the instant claims. Based on this, Applicants submit that **Paul et al.** does not identify the exact invention. The Applicants also submit that **Paul et al.** does not render obvious the instant invention as a person with ordinary skill in this art would not have a reasonable expectation that the claimed invention would work successfully. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of the rejection of claim 1 and dependent claims 8, 10-14, 16, 24 and 31 under 35 U.S.C. §102(a).

Non-statutory double patenting rejection

Claims 1, 6-8, 10-29, 71-75 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. PAT 6855528. Applicants respectfully traverse this rejection.

On page 9 of the Office Action, the Examiner states that Claims 1, 6-29, 71-75 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,855,528. The Examiner argues that although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1, 6-29, 71-75 herein and claim 1 of U.S. Patent No. 6,855,528 are both directed to a method of generating catalytic antibodies to polypeptide covalently reactive antigen comprising any antigenic polypeptide attached with any reactive covalently attached active center by inducing said antigen in organism such as mouse. The Examiner further states that claims 1, 6-29, 71-75 cannot be considered patentably distinct over claim 1 of U.S. Patent No. 6,855,528 when there is a specifically recited embodiment that would anticipate claims 1, 6-29, 71-75 herein. Alternatively claims 1, 6-29, 71-75 herein cannot be considered patentably distinct over claim 1 of U.S. Patent No. 6,855,528 that supports claim 1 of that application. U.S. Patent No. 6,855,528 teaches catalytic antibodies and methods of producing said antibodies using antigen PCRA wherein said antigen bind to antibody that is resistant to dissociation by 2% SDS. Based on this, the Examiner states that the embodiments fall within the scope of claims 1, 6-29, 71-75 herein and it would have been obvious to one having ordinary skill in the art to select the specific antigen analog comprising any antigenic polypeptide attached with electrophilic group and used in the method of claim 1 of U.S. Patent No. 6,855,528. Additionally, on pages 10-11, the Examiner states that these embodiments fall within the scope of claims 1, 6-29, 71-75 herein and it would have been obvious to one having ordinary skill in the art to select the specific antigen analog comprise any antigenic polypeptide attached with electrophilic group and used in the method of claim 1 of the US PAT 7338790 and the recited embodiments in the specification discussed above and pursue the inventions in the claims 1, 6-29, 71-75 of instant application. One having ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being a preferred embodiment within claim 1.

Claim 1 is amended as described supra. Applicants submit that U.S. Patent No. 6,855,528 teaches methods of producing covalently reactive antigen analog (CRAA), comprising 3-10 contiguous amino acids forming an epitope of a target antigen and further comprising a positively charged amino acid residue and an electrophilic reaction center. Applicants submit that the pCRA of the present invention and CRAA taught by Patent No. 6,855,528 are structurally distinct entities with differing reactivity to antibodies. Therefore, the antibodies produced and

isolated using the pCRA of the present invention will differ in their properties compared to the antibodies produced and isolated using the CRAA taught by U.S. Patent No. 6,855,528.

U.S. Patent No. 6,855,528 does not teach production of any amino acid that has a functional group to which, by means of an atom, covalent bond or linker, is attached a covalently reactive electrophilic group. Applicants submit that U.S. Patent No. 6,855,528 only teaches positively charged amino acids. In fact, U.S. Patent No. 6,855,528 only teaches covalently reactive antigen analog (CRAA), comprising 3-10 contiguous amino acids, and does not teach covalently reactive polypeptide antigen analogue (pCRA) comprising other antigenic determinants. In addition, U.S. Patent No. 6,855,528 does not teach water-binding groups and optional charged or neutral groups that enhance binding affinity and specificity.

Applicants submit that U.S. Patent No. 6,855,528 teaches a covalently reactive antigen analog (CRAA), comprising 3-10 contiguous amino acids forming an epitope of a target antigen and further comprising a positively charged amino acid residue and an electrophilic reaction center. The genus of pCRAs in the present invention includes conformational (discontinuous) electrophilic epitopes composed of spatially neighboring amino acids that are distant from each other in the linear sequence (represented as L1---Lx---Lm in the pCRA formula). For one skilled in the art, it is clear that the vast majority of antigenic epitopes in proteins are conformational epitopes. Therefore, the pCRAs have substantially greater utility than the CRAA taught by U.S. Patent No. 6,855,528. Further, U.S. Patent No. 6,855,528 does not teach a pCRA in which any amino acid that has a functional group to which, by means of an atom, covalent bond or linker, is attached a covalently reactive electrophilic group. Applicants submit that U.S. Patent No. 6,855,528 only teaches positively charged amino acids on the N terminal side of the electrophilic group. In comparison, a pCRA can contain the electrophilic group placed neighboring a positive, neutral or negative charged amino acid. In addition, U.S. Patent No. 6,855,528 does not teach water-binding groups and optional charged or neutral groups that enhance binding affinity and specificity.

The CRAA taught by U.S. Patent No. 6,855,528 must contain the electrophilic group within the peptide backbone as a replacement of a peptide bond in the polypeptide antigen. U.S. Patent No. 6,855,528 does not teach incorporation of the electrophilic group in a side chain functional group of the amino acids of a polypeptide. In contrast, the electrophilic group is located on the side chain functional group of any amino acid in the pCRA of the present invention. Thus, the teaching of U.S. Patent No. 6,855,528 is limited to a single electrophilic antigenic epitope within a small peptide produced by peptide synthesis. The genus of pCRAs in the present invention includes large proteins containing many electrophilic epitopes. One skilled

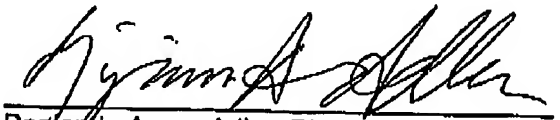
in the art is aware that incorporation of the electrophilic group in the side chain of one or more amino acid within the polypeptide is readily attainable. As the electrophilic group is attached to the side chains of various amino acids, a pCRA can be prepared from large proteins. One skilled in the art is aware that large proteins cannot be synthesized by purely chemical synthetic methods. Moreover, it is not possible to produce the post-translationally modified versions of native proteins by chemical synthetic means. In contrast, pCRAs can be prepared by modification of proteins that have been assembled by natural means, e.g., proteins purified from blood or from supernatants of cultured cells. Therefore, the pCRAs have substantially greater utility than the CRAA taught by U.S. Patent No. 6,855,528.

Applicants submit that U.S. Patent No. 6,855,528 does not render obvious amended independent claim 1 and dependent claims 6-29 and 71-75 as a person with ordinary skill in this art would not have a reasonable expectation that the claimed invention would work successfully. Accordingly, based on these remarks, Applicants respectfully request the withdrawal of the provisional rejection of claim 1 and dependent claims 6-29 and 71-75 under the judicially created doctrine of obviousness-type double patenting.

This is intended to be a complete response to the Office Action mailed January 30, 2009. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Only in the absence of Form PTO-2038, please debit all applicable fees from Deposit Account No. 07-1185, upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: July 30, 2009



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